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ROLE OF GST, TCF, ELMO1, TRPC1, IL-10 GENE POLYMORPHISM IN DIABETIC NEPHROPATHY

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ABSTRACT

There are about 40% of patients with type 1 and type 2 diabetes will develop diabetic nephropathy (DN), resulting in chronic kidney disease and potential organ failure. During the progression and development of DN, chronic elevated blood glucose (hyperglycaemia) together with glomerular hypertension leads to renal inflammation, progressive glomerulosclerosis and tubulointerstitial fibrosis resulting in organ failure. Genetic variants at a biomarker level could allow the detection of those individuals at high risk for diabetic nephropathy which could thus help in the treatment, diagnosis and early prevention of the disease. Current genome-wide relationship scans have recognized a number of chromosomal regions that possible include diabetic nephropathy susceptibility genes, and association analyses have evaluated positional applicant genes under these relation peaks. The possibility of increasing diabetic nephropathy is recovered several times by inheriting risk alleles at susceptibility loci of dissimilar genes like GST (glutathione-S-transferase), TCF (Transcription factor), ELMO1 (Engulfment and Cell Motility 1), *IL-10 (*Interleukin-10) and TRPC1 (transient receptor potential channel 1). The identification of these genetic variants at a biomarker level could thus, allow the detection of those individuals at high risk for diabetic nephropathy which could thus help in the treatment, diagnosis and early prevention of the disease.

KEYWORDS: Diabetes mellitus, Hyperglycemia, Diabetic nephropathy, Genetics, Biomarker, Genome-wide linkage

INTRODUCTION

Diabetic nephropathy is a kind of progressive kidney disease that occurs in people who have diabetes. Diabetic nephropathy (DN) is usually defined by macro-albuminuria—that is, a urinary albumin excretion of more than 300 mg in a 24-hour collection—or macro-albuminuria and irregular renal function as represented by an irregularity in serum creatinine, calculated creatinine authorization. It is a significant cause of morbidity in subjects with both insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). It is believed that Diabetic Nephropathy occurs as a result of the interplay of metabolic and haemodynamic factors in the renal microcirculation. The period of diabetes mellitus (DM), the stiffness of glycemic manages and blood pressure (BP) is certainly concerned. Hyper-glycaemia reparation tissue via the accumulation of advanced glycation end-products (AGEs), the creation of isoform(s) of protein kinase C (PKC) and the activation of aldose reductase (1).

Association Of Risk Factor In Diabetic Nephropathy

Every people with diabetes have a risk of increasing diabetic kidney disease. However, a large investigates trial showed that there are certain factors that increase the risk of developing this condition. A reduced control of your blood sugar (glucose) levels. (The greater your HbA1c level, the better your risk. The duration of time you have had diabetes. The heavier you become. Having elevated blood pressure. The higher your blood pressure, the bigger your risk. If you are male, this means that having a good manage of your blood glucose level, keeping your weight in check and treat high blood pressure will reduce your risk of increasing diabetic kidney disease. If you have early diabetic kidney disease (microalbuminuria), the risk that the disease will become inferior is increased with the poorer the control of blood sugar levels. The better your HbA1c level, the greater your risk.

Association of High Glucose in Diabetic Nephropathy

Hyperglycaemia is a main stimulus for the growth of nephropathy in both type 1 and type 2 diabetes, and the most effective way to reduce the risk of diabetic complications is to continue optimal glycemic manage (2). Increased glucose flux during the hexosamine and polyol pathways, oxidative pressure and overproduction of AGEs. This increase in absorption of intermediates leads to increased start of PKC

isoforms, increased production of AGEs, and accelerate glucose flux through the polyol and hexosamine pathways. Role of several genes factor in diabetic nephropathy are discus given below.

Role of GST (Glutathione-S-transferase)

The GSTs are a multigenic super family of detoxification enzymes that are important for cell protection against oxidative break, as well as the biotransformation of xenobiotics, due to their acting on a wide variety of substrates, mediating the conjugation of reduced glutathione to electrophilic species which leads to the elimination of toxic compounds (3-4). GST enzymes are concerned in the combination of inflammatory mediators, leukotrienes and prostaglandins and act also in cell signaling pathway as potential regulators of apoptosis. Regarding their role within oxidative stress, GSTs detoxify some of the secondary ROS generated during oxidation of membranes or other cellular constituents. GSTs act in the detoxification of organic hydroperoxides and protect cells from peroxide-induced cell death (5). There are two theta class genes, GSTT1 and GSTT2, located on chromosome 22. GSTT1 is represented by two alleles: A functional or wild allele (GSTT 1 * 1) and a nonfunctional or null allele (GSTT1*0). The homozygous genotype for the null allele has been defined as GSTT 1*0 and the genotype with at least one efficient allele has been denoted as GSTT 1*1.The GSTT 1*0 frequency ranges from 16% to 38% of the overall population (6). According to substrate specificity, chemical affinity, structure, sequence, and kinetic behavior, few classes of soluble GSTs have been identified (alpha, kappa, mu, pi, theta, zeta, omega, and sigma). The most researched one is glutathione S-transferase mu 1 (GST M1) enzyme in GST M class with its gene located in Chromosome 1p13.3 and glutathione S-transferase theta 1 (GST T1) enzyme in GST T class with its gene located in Chromosome 22q11.23. It has been shown that individuals moving the null genotype of GST have radically reduced activity of this enzyme compare to wild genotype carriers (7). According to recent studies, GST T1 and M1 are regarded as candidate polymorphisms for susceptibility to type 2 diabetes (T2D) (8) or chronic diabetic complications (9). The majority of studies have focused on adult subjects with T2DM; only one collective of authors has targeted young subjects with T1D (10). Among the most important human classes of this system, GSTM1 and GSTT1 genes display a deletion polymorphism that leads to a lack of active isoforms when in homozygosis, known as the null genotype (3). In the case of GSTT1-null, which occur at frequencies of 11–38% in different populations, 50 kb of genomic series containing the entire gene is deleted. While for the GSTM1-null, changeable frequencies have a range of 20–70%, involving a 15-kb sequence deletion (3-4,11-12).

Role of TCF (Transcription Factor)

As a factor 7 (specific T cells, HMG-box) transcription also known as TCF7L2 or TCF4 is a protein that acts as a transcription factor. In humans, this protein is encoded by the TCF7L2 gene (13-14). The single nucleotide polymorphism (SNP) in the TCF7L2 gene, rs7903146, is, to date, associated with the risk of type 2 diabetes genetic marker (15) the most significant (DT2). NPP in this gene are associated with a increased risk of type 2 diabetes (16) and gestational diabetes (17). CTF7L2 is a transcription factor that influences the transcription of many genes thus exerting a variety of functions within the cell. Member of the Wnt signaling pathway Wnt signaling pathways are a group of signal transduction proteins that pass signals to a cell through cell surface receptors. Passing the pathway leads to the Î²-catenin section with BCL9, translocation to the nucleus, and the association with TCF7L2 (18) which in turn leads to the activation of Wnt target genes in specifically repressing the synthesis of the proglucagon in endocrine cells (16,19). The gene codes for TCF7L2 a transcription factor involved in the Wnt signaling pathway, which plays an important role in the development of pancreatic islets and adipogenesis (20). heterodimers form TCF7L2 with b-catenin, which induces the expression of different genes, including insulin peptide 1 (GLP-1), the insulin gene and other genes that encode proteins involved in processing and exocytosis of granules of insulin (21-24). As GLP-1 and insulin play a key role in blood glucose homeostasis, it has been hypothesized that the TCF7L2 variants can change the sensitivity of type 2 diabetes indirectly reduce GLP-1 secretion by endocrine cells (25). Furthermore, as the Wnt pathway appears to be important for pancreas development during embryonic growth, it is also possible that beta cell mass, beta pancreatic cell development and / or beta cell function also are affected by this pathway (26). However, the exact molecular mechanism section polymorphisms DM2 TCF7L2 not yet clarified (26-27).

Role of ELMO1 Gene (Engulfment and Cell Motility 1)

ELMO1 (immersion and cell motility 1) as a new candidate and powerful gene, located on chromosome 7p14.2-14.1, is used for cell motility and phagocytosis of apoptotic cells (28). However, the precise role of ELMO1 in the development and progression of nephropathy attributed to T2D is still unknown. They evaluated more than 80 000 SNP loci and SNP loci in the 18 intron gene ELMO1 was found to be strongly

associated with diabetic nephropathy (29). Subsequent functional studies have shown an increase in ELMO1 expression in the presence of high glucose. To support a potential role in the pathogenesis of diabetic nephropathy, cell adhesion inhibited ELMO1 term, while promoting the growth of β-transcription factor, type 1 collagen, fibronectin and integrin-related kinase expression (29-30). Recently large African-American cohort with type 2 diabetes have suggested that the SNP locus in the gene 13 introns ELMO1 was found associated with DN (31). Complications of T2D were more common in Asians demonstrated by Westerners (32). ELMO1 plays a physiopathological role in the development of albuminuria and changes the characteristics of fibrotic tissue of diabetic nephropathy.

Role of IL-10 (Interleukin-10), Gene

The IL-10 gene is located on chromosome 1q31-1q32 and encodes a protein having a molecular weight of 4.7 x 103. The IL-10 family of cytokines has nine members produced by cells, IL-10, IL 19, IL- 20, IL-22, IL-24, IL-26, IL-28A, 28B and IL-IL-29 and four viral homologues. IL-10 is produced by multiple subpopulations of T cells such as Th2 and regulatory T lymphocytes (Treg), NK cells and various types of cells, including macrophages, dendritic cells and B cells in the kidney, IL-10 is mainly secreted by mesangial cells and endothelial. Viral homologues of IL-10 may be produced by the virus, cytomegalovirus, ORF and Epstein-Barr to herpesvirus 2 (32-34). In fact, the IL-10 gene SNP -1082G / A is more common in patients with IgA nephropathy and focal segmental glomerulosclerosis and is associated with a worse prognosis of the disease (35). IL-10 plays an important role in normal renal physiology and in acute renal injury and progression of chronic renal failure. Mesangial cells are the main local source of IL-10 in the normal adult kidney (36). mesangial cells are the main regulators of renal function, since (1) provide structural support to the glomerulus by secretion and maintenance of the extracellular matrix; (2) modulating the size of the glomerular capillaries, which affects the glomerular filtration rate; and (3) serve as a source and destination for many growth factors (37-38). In the healthy adult kidney, the renewal of the mesangial cell is always under strict control. High levels of circulating IL-10 have been reported in diabetic patients. Furthermore, serum IL-10 levels of serum albuminuria have been predicted and correlated with the severity of diabetic nephropathy (39).

Role of TRPC1 (Transient Receptor Potential Channel 1)

Transient receptor potential (TRP) proteins are non-selective transient receptor potential channel. TRP proteins perform various functions such as mobile and versatile effector sensors (40). TRPC1 (potential transient canonic receptor 1), widely expressed in many cell types, is a Ca2 + channel permeable cation involved in various physiological functions (41). Since Ca2 + has been shown to play a key role in the insulin secretion of islets of Langerhans and homeostasis of altered Ca2 + cells may be involved in defective insulin release (42), is a molecule key signaling "induction dementia, and an increased risk of dementia in patients with diabetes (43) was observed. Interestingly, TRPC1 activity is positively associated with vascular smooth muscle cell proliferation (VSMC) and intimal hyperplasia, which play a critical role in the development of DN (44). While TRPC1, decreased in the kidneys of diabetic animal models, may play a key role in the progression of diabetic nephropathy (45). Mechanism of TRPC1 can contribute to the development of diabetic nephropathy has not yet been clarified. The gene on chromosome 3q22-24 TRPC1 located in the binding zone with diabetic nephropathy. Therefore, TRPC1 represents a potent biological and positional candidate for diabetic nephropathy. This study was designed to examine the potential protective effects of transient receptor-like canonic type 1 (TRPC1) in diabetic nephropathy.

CONCLUSION

In conclusion, the hunt for genes contributing to the development of diabetic nephropathy has begun recently. In order to uncover its genetic background, it is indispensable to identify gene loci and to test specific candidate genes and possibly their interaction. the distribution of GST, TCF, ELMO1, INTERLEUKIN-10 and TRPC1 gene polymorphisms in patients with type 2 diabetes mellitus and controls in order to explore the possible association between GST variant and the amount of type 2 diabetes mellitus and also to evaluate the role of these polymorphic genes as a genetic risk modifier in the etiology of type 2 diabetes mellitus and the levels of blood lipids.

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